

removed. Theophylline, phenobarbital and digitoxin generally fit these criteria. Conversely, digoxin and tricyclic antidepressants such as imipramine have large volumes of distribution and show limited removal by charcoal. Overall, the principles that govern the ability of oral activated charcoal to increase the clearance of drugs and poisons from the body are analogous to the principles that govern the effectiveness of hemodialysis and hemoperfusion for removing drugs and poisons. Major exceptions to this generalization are drugs and poisons that are not adsorbed by charcoal or that do not enter the gut from the blood. For example, we would not expect aminoglycoside antibiotics to be effectively removed since they do not cross the gut membrane, as evidenced by lack of absorption when they are administered orally.

Of course, this model for increasing drug clearance with activated charcoal assumes that adequate charcoal is given to fill the gut lumen.¹ This is done generally by giving doses of approximately 20 grams of superactivated charcoal every two hours for maximum effect.¹ Activated charcoal can also be used as an adsorbent in hemoperfusion systems to increase the clearance of drugs, but this is beyond the scope of this editorial.⁴

In summary, there is no question that charcoal given orally, especially superactivated charcoal, can decrease the absorbance of many drugs from the gut and, in many cases, increase the clearance of drugs from the body, sometimes substantially. Thus, there is no doubt about the pharmacokinetic efficacy of charcoal as both an adsorbent and a substance to increase clearance. What has never been clearly established, however, is that these impressive pharmacokinetic properties of charcoal are, in fact, related to better patient outcome.⁵ Derlet and Albertson in their review discuss this important point and we would reemphasize this question. First principles in pharmacology and medicine would strongly suggest, that, if less drug or intoxicant is absorbed, the patient will have less of a toxic reaction; or, if the drug or intoxicant is more rapidly removed, the patient will suffer less adverse effects. This should result in less morbidity—that is, shorter times in intensive care units. These assumptions, however, remain to be established conclusively in controlled clinical trials.

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Need Kidneys Fail?

THE RATE OF PROGRESSION to end-stage renal failure is not influenced solely by the extent and severity of the primary renal insult. Amplifiers of risk include systemic hyperten-

sion, urinary tract infection or obstruction and intrarenal deposition of calcium and urate salts. Often, however, despite control of these risk factors, mild but permanent kidney injury eventually results in progressive deterioration of renal function. These observations suggest that reduction of the number of functioning nephrons beyond a certain point ultimately leads to failure of the remaining nephron units. Investigation into the mechanism(s) responsible for this process in animals has shown that progressive loss of these residual nephrons is a predictable consequence of the glomerular hemodynamic response to renal injury and, in particular, to the adaptive increase in glomerular capillary hydraulic pressure that regularly follows a decline in the number of functioning nephrons.¹ Some of the evidence upon which our hypothesis is built is reviewed by Avasthi elsewhere in this issue.

A pattern of progressive azotemia, proteinuria and glomerular sclerosis similar to that found in animals after partial renal ablation is also observed in clinical settings following a circumscribed renal injury. These include bilateral renal cortical necrosis and vesicoureteral reflux. Likewise, acute poststreptococcal glomerulonephritis and the various forms of lupus nephritis occasionally progress to chronic renal failure in the absence of continued immunologic injury. Hemodynamic factors may also explain the observation that pregnancy, with its attendant increments in glomerular filtration rate and renal blood flow, frequently accelerates a loss of renal function in women with preexisting kidney disease.

These observations therefore urge the answering of a number of clinical questions. First, what degree of renal mass reduction in humans results in progressive glomerular disease? Some information in this regard is available from studying cases of the congenital renal disease, oligomeganephronia, a condition characterized by a reduction in nephron number to approximately 20% of the normal complement and by pronounced hypertrophy of those nephrons present. Hyperfiltration per nephron in this disorder initially maintains the total glomerular filtration rate at an acceptable level, but by adolescence children with this condition typically have progressive proteinuria, glomerular sclerosis and renal failure. More common is unilateral renal agenesis, where glomerular hyperfiltration in a solitary kidney maintains renal function at near-normal levels during childhood, only to eventuate in the development of renal failure in early adult life in some affected persons. It would thus appear that a reduction of renal mass by half or more during very early life imposes a risk, as yet unquantified, for subsequent hemodynamically mediated overt renal injury.

A second important question is whether increased glomerular capillary pressures can initiate progressive glomerular disease even when the number of functioning nephrons is normal. We have suggested that the protein-rich diet characteristic of modern Western society may induce chronic renal hyperperfusion and hyperfiltration, thereby contributing to the glomerulosclerosis seen with aging.¹ The recent observation that clinically overt proteinuria and renal insufficiency are more likely to develop in those patients with type I diabetes who have substantial hyperfiltration early in the course of their disease than in those patients with lesser initial degrees of hyperfiltration also supports an affirmative answer to this question.² Additional support is found in sickle cell anemia, which, although classically associated with papillary

ischemia, is also characterized by greatly elevated renal blood flow and filtration rates during the first decade of life, followed by a gradual loss of renal function and widespread glomerular sclerosis by the third decade.³

Standard treatment modalities for chronic renal insufficiency do little to impede this relentless hemodynamic process. But several strategies aimed at interrupting the underlying hemodynamic events, or subsequent steps in the injury process, might serve to forestall the otherwise predictable progression to end-stage renal disease. Restriction of dietary protein has been shown to substantially slow and perhaps even halt the progression of many forms of chronic renal disease in humans.^{4,5} Evidence suggesting that treatment of hypertension also slows this progression has likewise been reported, including the recent demonstration in diabetic animals that antihypertensive therapy with a potent angiotensin I-converting enzyme inhibitor provides substantial protection against glomerular injury even when the drug is administered to animals that do not display systemic hypertension.⁶ It should be recognized, however, that not all antihypertensive regimens successful in reducing systemic arterial pressure result in an equivalent lowering of glomerular capillary pressure,⁷ and it therefore becomes of paramount importance in treating systemic hypertension in patients with underlying renal vasodilatation to construct a medical regimen specifically designed to alleviate intraglomerular hypertension. At our present state of knowledge, this challenge seems best met by the use of converting enzyme inhibitors. Strict metabolic control in patients with diabetes, achieved by continuous insulin infusion or other means and instituted early in the disease's course, could likewise prove effective in preventing glomerulopathy. Such tight control, however, is difficult to

achieve widely and therefore renders an aggressive lowering of blood pressure and avoidance of excessive dietary protein mandatory adjuncts in the management of these patients.

A final question that derives from these earlier considerations concerns the appropriate time for initiating potentially beneficial therapy. With a 50% reduction in the glomerular filtration rate, the serum creatinine concentration increases only slightly, but even this slight increment reflects a tremendous insult to the overall nephron population. It is therefore essential that institution of therapy for patients at risk for hemodynamically mediated renal injury not await documentation of more severe functional compromise, but should precede these impairments and thereby delay if not avert them.

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